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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/634,663
Filing Date: August 05, 2003
Appellant(s): SMITH ET AL.

Robert Barrett
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 08 October 2008 appealing from the Office action mailed 05 June 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 5,935,847	Smith et al	10 August 1999
US 5,912,177	Turner et al	15 June 1999
US 6,759,245	Toner et al	06 July 2004
US 5,686,304	Codner, Meryl	11 November 1997
US 5,989,215	Delmotte et al	23 November 1999

Smith is directed to a cell culture container comprising flexible walls characterized by a gas permeability sufficient to permit cellular respiration. The flexible walls are formed in part from ethylene vinyl acetate copolymer, and are arranged to facilitate the culture of adherent cells.

Turner is directed to a cell culture container comprising flexible walls and an inner surface formed from a fibrin matrix layer.

Toner is directed to a system that includes an ethylene vinyl acetate membrane upon which a fibrin layer is positioned to accommodate adherent cells.

Codner is directed to a flexible cell culture container that comprises sidewalls with inner surfaces formed from ethylene vinyl acetate copolymer.

Delmotte is directed to a fibrin delivery device capable of administering a fibrin layer upon a surface.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1, 3-11, 19-21, 23-34 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5935847) in view of either Toner (US 6759245) or Turner (US 5912177), and further in view of Codner (US 5686304).

With respect to claims 1 and 48, Smith discloses a closed cell culture container (Figure 2:20) comprising a first flexible sidewall (Figure 2:22) connected to a portion of an opposing second flexible sidewall (Figure 2:24) along a peripheral seal to define a containment area (Figure 2:26). This is disclosed in column 6, lines 12-33. Column 2, lines 24-31 and column 3, line 59 to column 4, line 46 teach that the first and second sidewalls are constructed from flexible polymeric materials that permit cellular respiration. Column 5, lines 39-45 indicate that the sidewalls are constructed from ethylene vinyl acetate. A polystyrene layer (Figure 2:12) is provided to promote cell adhesion to the inside surface of the culture container. Smith, however, does not expressly state that a fibrin matrix layer is positioned on a portion of the interior surface of the first or second sidewalls of the cell culture container.

Toner discloses a cell culturing device (Figure 1) that includes a chamber divided by a gas permeable, liquid impermeable polymeric membrane (Figure 2:30). Cells (Figure 2:40) are seeded upon the membrane, and gases from an oxygenated liquid stream (Figure 2:20) are allowed to diffuse through the membrane in order to contact the cells. This is disclosed in column 3, lines 1-25 and column 7, line 10 to column 8, line 19. Column 9, lines 8-42 indicate that the membrane may be constructed from a variety of polymer compounds, including ethylene vinyl acetate, arranged in a single or multi-layered assembly. Column 11, lines 27-56 teach that the membrane (Figure 1:30) is coated with a fibrin matrix layer (Figure 1:41) to increase cell adhesion.

Turner discloses a polymer bag that forms a closed container for holding a cell culture. Column 3, lines 47-65 state that the bag is permeable to gases vital for cellular metabolism. Column 2, lines 43-50 indicate that a fibrin matrix is immobilized upon the inner walls of the bag in order to facilitate the adhesion of cells.

Smith, Toner and Turner are analogous art because they are from the same field of endeavor regarding cell culture containers.

At the time of the invention, it would have been obvious to include a fibrin matrix layer positioned on the interior surface of the polystyrene layer disclosed by Smith. In column 6, line 65 to column 7, line 19, Smith teaches that it is desirable to provide a culture vessel which includes sidewalls that are capable of accommodating adherent dependent cells. Toner and Turner each teach that fibrin, when applied to a polymer substrate, will enhance cell immobilization to the polymer substrate. In this way, Smith's invention would be improved through the addition of a fibrin matrix layer because the fibrin matrix would allow the cell culture container to better accommodate a wider range of adherent dependent cell types.

The combination of Smith and Toner/Turner still differs from Applicant's claimed invention because it is not entirely clear if the inner surface of Smith's container comprises an ethylene vinyl acetate copolymer. The Figures predominantly indicate that the inner surface of the container is covered by a polystyrene layer (Figure 8:28) as opposed to an ethylene vinyl acetate copolymer layer (Figure 8:24).

Codner discloses a cell culture apparatus. In column 6, line 53 to column 7, line 5, Codner teaches that the walls defining the apparatus comprise an inner surface formed from an ethylene vinyl acetate copolymer.

Smith, Toner, Turner and Codner are analogous art because they are from the same field of endeavor regarding cell culture bags.

At the time of the invention, it would have been obvious to construct the inner sidewalls of the Smith culture bag from ethylene vinyl acetate copolymers. Codner is evidence that it is well known to achieve optimum cell growing conditions using this material. In applying the fibrin matrix disclosed by Turner and/or Toner, one of ordinary skill in the art would have understood to either supplement the existing polystyrene layer of Smith with fibrin or replace the polystyrene layer completely. Polystyrene and fibrin are considered to be functionally equivalent in that both are capable of fostering the growth of adherent cells.

With respect to claims 3 and 4, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith teaches in column 4, lines 11-46 that the gas permeable material is either EVA, polyolefin, polyamide or styrene. The polymeric material of the first sidewall is a styrene and hydrocarbon multi-component polymer blend.

With respect to claims 5-11, 49 and 50, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith teaches that the gas permeable material is either a monolayer or a multilayer structure. Monolayer cell culture

containers are well known in the art, and Figures 1 and 4 illustrate multilayer embodiments. A polystyrene layer (Figure 4:12) and a skin layer (Figure 4:18) are provided in addition to the substrate layer (Figure 4:14). Column 5, lines 7-18 teach that the skin layer and substrate layer are formed on the outer surface of the polystyrene layer, so that the inner surface of the polystyrene layer forms the interior surface of the culture chamber. The skin layer is formed from polyethylene copolymers and polypropylene copolymers. Column 4, lines 11-46 indicate that substrate layer is anywhere from 0-40% ethylene vinyl acetate copolymer. It is an intrinsic feature of the invention that the composition of the substrate and polystyrene layers can be manipulated in order to achieve any desired polymer distribution.

The claimed weight ratios are simply result effective variables. In the absence of new or unexpected results, it would have been obvious to optimize the composition of the substrate and skin layers. This optimization could simply be accomplished by producing different compositions and testing their ability to be used in cell culturing. See *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

With respect to claims 19-21, 23-26 and 51-53, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith states in column 2, lines 24-31 that the polystyrene layer (1st layer) has a thickness within the range of 0.0001 inches to 0.001 inches. Column 4, lines 47-56 indicate that the substrate layer (2nd layer) has a thickness of 0.004 inches to 0.025 inches. Column 4, lines 11-46 teach that the second layer is a multi-component polymer blend that includes styrene and hydrocarbon copolymer. Figure 2 indicates that the gas permeable EVA material is used in the construction of both the first and

second sidewalls. The nature of the invention regarding copolymer content and layer thickness has already been described.

With respect to claims 27-32, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith states in column 2, lines 39-51 that the culture container has a oxygen permeability of 9-15 Barrers, a carbon dioxide permeability of 40-80 Barrers, a nitrogen permeability of 10-100 Barrers and a water vapor transmission rate of less than 20 (g mil/100 in^2/day). Column 5, line 49 to column 6, line 8 indicates that the first and second sidewalls have a flexural modulus of 10,000-30,000 psi, and that the sidewalls are optically clear. The container is radiation sterilizable. Column 7, lines 39-44 indicate that at least one port (Figure 9:40) provides access to the containment area.

With respect to claims 34 and 35, Smith, Toner/Turner and Codner disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In addition, Smith states in column 6, line 66 to column 7, line 19 that the inside surfaces of the culture container can be modified in order to determine to what areas cells are allowed to adhere. Accordingly, it would have been obvious to apply the fibrin matrix disclosed by Toner to any part of the container surface that is desired to promote cell adhesion. This intrinsically could pertain to the entire inner surface of the container, or just specific regions of the inner surface. If the culture container is intended to facilitate the growth of adherent cell types, then it would be obvious to apply the fibrin matrix to the entire sidewall interior surface. If the culture container is intended to facilitate the growth of

adherent and non-adherent cell types, then it would be obvious to apply to fibrin matrix to just a part of the sidewall interior surface.

2) Claims 36-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5935847) in view of Toner (US 6759245)/Turner (US 5912177) and Codner (US 5686304) as applied to claim 1, and further in view of Delmotte (US 5989215).

With respect to claims 35-37, Smith, Toner/Turner and Codner disclose the invention set forth in the 35 U.S.C. 103 rejections above, however do not expressly disclose the nature of the fibrin matrix.

Delmotte discloses a method for forming a fibrin matrix that includes delivering a first solution of fibrinogen and factor XIII and a second solution of thrombin and calcium to a desired surface. This is disclosed in column 3, lines 31-44 and column 8, lines 3-15. In column 12, line 34 to column 13, line 20, Delmotte states that the amount of thrombin added to the fibrinogen solution is directly related to the pore size of the fibrin matrix product. Thrombin can be added in varying amounts in order to create a fibrin network characterized by pore diameters anywhere between 0.2-4 microns.

Smith, Toner/Turner, Codner and Delmotte are analogous art because they are from the same field of endeavor regarding cell culture systems.

At the time of the invention, it would have been obvious to form a fibrin matrix within the cell culture container disclosed by Smith and Toner by mixing a solution of fibrinogen with a solution of thrombin. In column 4, line 57 to column 5, line 16, Delmotte states that by separating fibrinogen and thrombin into two separate solutions, one is able to more easily

manipulate the concentrations of fibrinogen and thrombin to effect change in the characteristics of the resultant fibrin film. In this way, the concentration of thrombin can be readily changed in order to create a fibrin matrix with a desired pore size.

With respect to claims 38-46, Smith, Toner/Turner, Codner and Delmotte disclose the apparatus set forth in the 35 U.S.C. 103 rejection above. In column 7, lines 29-32, Delmotte teaches that the components of the fibrinogen and thrombin are derived from human plasma. It would have been obvious to utilize recombinant components of fibrinogen and thrombin, as well. When the fibrin matrix is used in a bioreactor and not for treating a human being, it is less important to use fibrinogen and thrombin attained from human blood plasma. Techniques for creating recombinant biomolecules are well known in the art.

With respect to claim 47, Smith, Toner/Turner, Codner and Delmotte disclose the apparatus set forth in claim 37 as set forth in the 35 U.S.C. 103 rejection above. In addition, Delmotte discloses in column 8, lines 3-29 that fibrin is made from a first solution containing 10-40 IU/ml of fibrinogen and factor XIII, and a second solution containing 3-10,000 IU/ml of thrombin and 45 micromoles/ml of calcium. Column 15, lines 1-15 disclose a method in which the fibrinogen and thrombin solutions are repeatedly applied to a surface in 0.3 ml increments. Column 18, lines 51-63 disclose a method in which 3.5 ml of the fibrinogen and thrombin solutions are mixed to form a fibrin matrix. The fibrinogen and thrombin solutions are incubated, and the formed fibrin matrix has a pore size of anywhere between 0.2-4 microns.

(10) Response to Argument

I. Claims 1, 3-11, 19-21, 23-34 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5935847) in view of either Toner (US 6759245) or Turner (US 5912177), and further in view of Codner (US 5686304).

Appellant's principle arguments are

(a) Smith, Toner and Turner fail to disclose or suggest a flexible interior surface comprising an ethylene vinyl acetate copolymer. Smith, Toner, Turner and Codner also fail to disclose or suggest a fibrin matrix layer on a portion of the ethylene vinyl acetate copolymer interior surface.

In response to Appellant's arguments, please consider the following comments.

The Smith reference discloses a flexible cell culture bag that comprises an ethylene vinyl acetate (EVA) copolymer layer (Figure 2:14). It is agreed that this EVA layer does not represent an inner surface because it is coated by a polystyrene layer (Figure 2:12) to promote cell adhesion. However, since Toner and Turner both teach that fibrin is also known in the art as an effective material to facilitate cell immobilization, one of ordinary skill in the art would have found it obvious to replace the polystyrene layer with a fibrin layer. Once the polystyrene is removed from the Smith bag, the pre-existing EVA layer would become the inner layer, which would in turn be coated over by fibrin.

Toner particularly points out that fibrin is compatible with EVA materials. Column 9, lines 26-42 of Toner state that the membrane upon which the fibrin is applied is formed from EVA. Upon review of Toner, one of ordinary skill in the art would be motivated to replace the

polystyrene layer of Smith with fibrin because Toner teaches that fibrin is not only biocompatible, but also readily combined with an EVA base layer.

Codner is provided as additional evidence that it is known in the art to utilize cell culture bags formed from a polymer material comprising an EVA inner surface. Upon review of Codner, one of ordinary skill in the art would be motivated to start with a cell culture bag comprising an EVA inner surface, and then utilize any additional treatments (such as fibrin application) as deemed necessary.

(b) Smith only teaches using ethylene vinyl acetate as a substrate layer 14, which represents an outer layer. Smith is entirely directed to an interior cell growth layer composed of polystyrene (not EVA).

In response to Appellant's arguments, please consider the following comments.

As noted above, one of ordinary skill in the art would understand to replace the polystyrene layer disclosed by Smith with the fibrin matrix disclosed by Turner and Toner. Fibrin and polystyrene are both effective in accommodating the immobilization of adherent cells, and therefore are considered to be functionally equivalent and interchangeable. Replacement of the Smith polystyrene layer with fibrin would result in the inner wall surface being formed from EVA copolymer with a fibrin coating. This arrangement would be structurally sound and suitable for cell growth, as evidenced by the Codner reference which indicates that cell culture bags comprising EVA inner wall surfaces are well known in the art.

(c) Although Turner discloses a flexible cell culture bag comprising a fibrin coating, Turner fails to disclose the use of ethylene vinyl acetate copolymer.

In response to Appellant's arguments, please consider the following comments.

Turner is not relied upon for the disclosure of EVA. Smith already describes the use of EVA throughout the reference. Codner also discloses the use of EVA sidewalls in column 6, lines 53-58. Toner likewise discloses the use of an EVA membrane coated by fibrin in column 8, line 57 to column 9, line 42.

(d) Codner fails to disclose a fibrin matrix on a portion of an ethylene vinyl acetate copolymer interior surface.

In response to Appellant's arguments, please consider the following comments.

Codner is not relied upon for the disclosure of fibrin. As described above, Turner and Toner each teach that it is known in the art to provide a fibrin matrix to improve the culture of adherent cells. Codner is merely relied upon for teachings regarding the widespread use of EVA in the cell culture bag art.

(e) Toner teaches away from combination with Smith by teaching a device having a completely different operation than Smith. Toner is directed to a device having rigid and impermeable cell walls, whereas Smith is a flexible, gas-permeable bag.

In response to Appellant's arguments, please consider the following comments.

It has never been suggested that it would be obvious to transform the flexible bag of Smith into a rigid, impermeable container. Rather, it has been submitted that one of ordinary

skill in the art would have been motivated to include a fibrin layer in the existing bag structure of Smith.

Regardless, Applicant's argument is misleading because even though Toner does teach a rigid outer container, the part that is coated by fibrin is actually a flexible, gas-permeable membrane (Figure 2:30) formed from EVA (just like the sidewalls of Smith). It is therefore submitted that, in regard to the actual cell culture surfaces of both Smith and Toner are very similar.

(f) Smith explicitly teaches away from an interior surface comprising an ethylene vinyl acetate by stating that "the decay of the charge on EVA will render the container ineffective for growing adherent cells."

In response to Appellant's arguments, please consider the following comments.

The proposed combination of Smith with Toner and Turner would not result in a cell culture container in which EVA inner sidewalls directly interact with adherent cells. Rather, the combination would comprise a fibrin matrix suitable for cell growth. The fibrin matrix would serve as a substitute for the polystyrene layer of Smith. Smith only teaches away from the use of EVA *and nothing else*, however the proposed combination would provide a fibrin matrix layer capable of enhancing cell growth.

(g) Toner teaches away from a closed culture container because Toner is directed to an open or flow-through cell-culturing device.

In response to Appellant's arguments, please consider the following comments.

It is agreed that Toner discloses an open, flow-through cell-culturing device. However, Toner is devoid of any statement indicating that it is impractical to utilize a fibrin matrix layer in a closed, bag-like system (as taught by Smith). Toner gives no reason to believe that fibrin would prove to be incapable of facilitating cell growth in the system of Smith. To the contrary, the Turner reference has been cited as evidence that fibrin is effective in accommodating cell adhesion in bag-like systems.

II. Claims 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (US 5935847) in view of Toner (US 6759245)/Turner (US 5912177) and Codner (US 5686304) as applied to claim 1, and further in view of Delmotte (US 5989215).

(a) The physical structure of the fibrin delivery system disclosed by Delmotte is incompatible with the system of Smith. The syringes of Delmotte are rigid and impermeable, whereas the container of Smith is flexible and gas-permeable.

In response to Appellant's arguments, please consider the following comments.

Delmotte is not relied on for teachings regarding the use of any particular type of fibrin delivery means. Rather, Delmotte is as evidence that it is known in the art to form a fibrin matrix by delivering a first solution of fibrinogen and factor XIII and a second solution of thrombin and calcium to a desired surface. Delmotte states that the amount of thrombin added to the fibrinogen solution is directly related to the pore size of the fibrin matrix product. Thrombin can be added in varying amounts in order to create a fibrin network characterized by pore diameters anywhere between 0.2-4 microns.

In following the teachings of Delmotte to create a fibrin material for use in the apparatus of Smith, one of ordinary skill in the art would understand that it is irrelevant whether or not Delmotte also describes a rigid and impermeable container. The nature of the Delmotte container and the formation of a desirable fibrin layer are entirely unrelated. Claims 36-43 include limitations entirely drawn to the composition of the fibrin layer, and have nothing to do with the exterior sidewalls of a cell culture device.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Nathan A Bowers/
Examiner, Art Unit 1797

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Supervisory Patent Examiner, Art Unit 1797

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